

TITLE: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

INVENTOR'S NAME: David J. Grainger, et al.

SERIAL NO.: 09/150,813 DOCKET NO.: 1543.002US1

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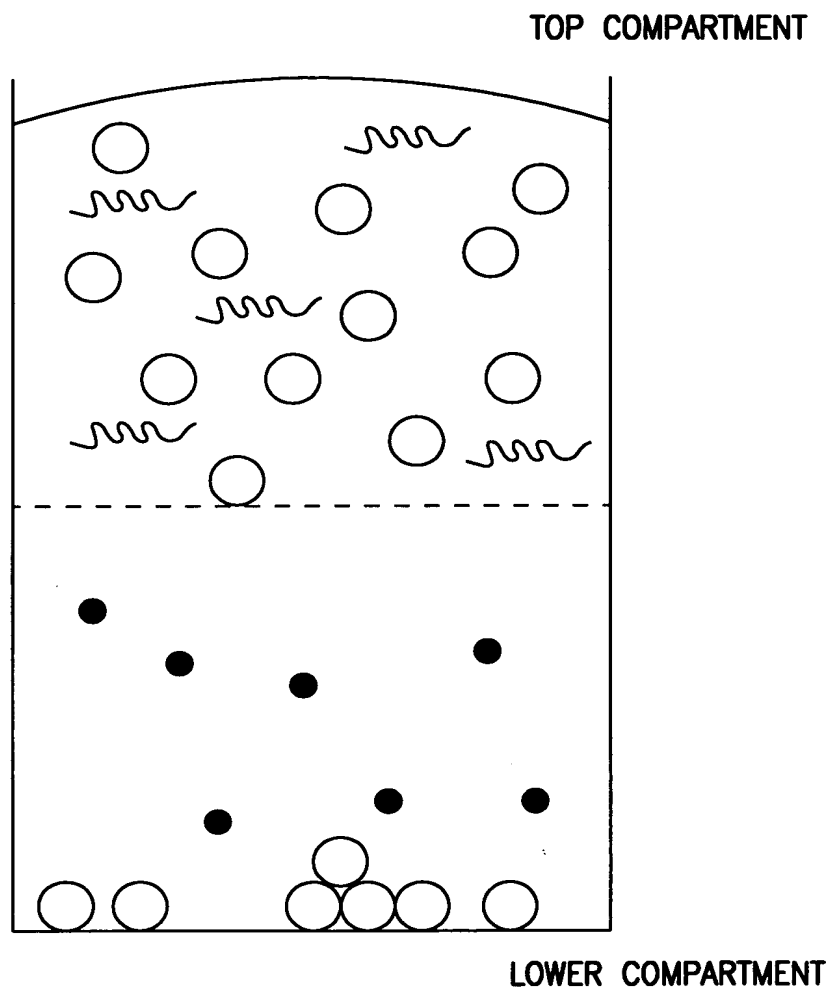


FIG. 1

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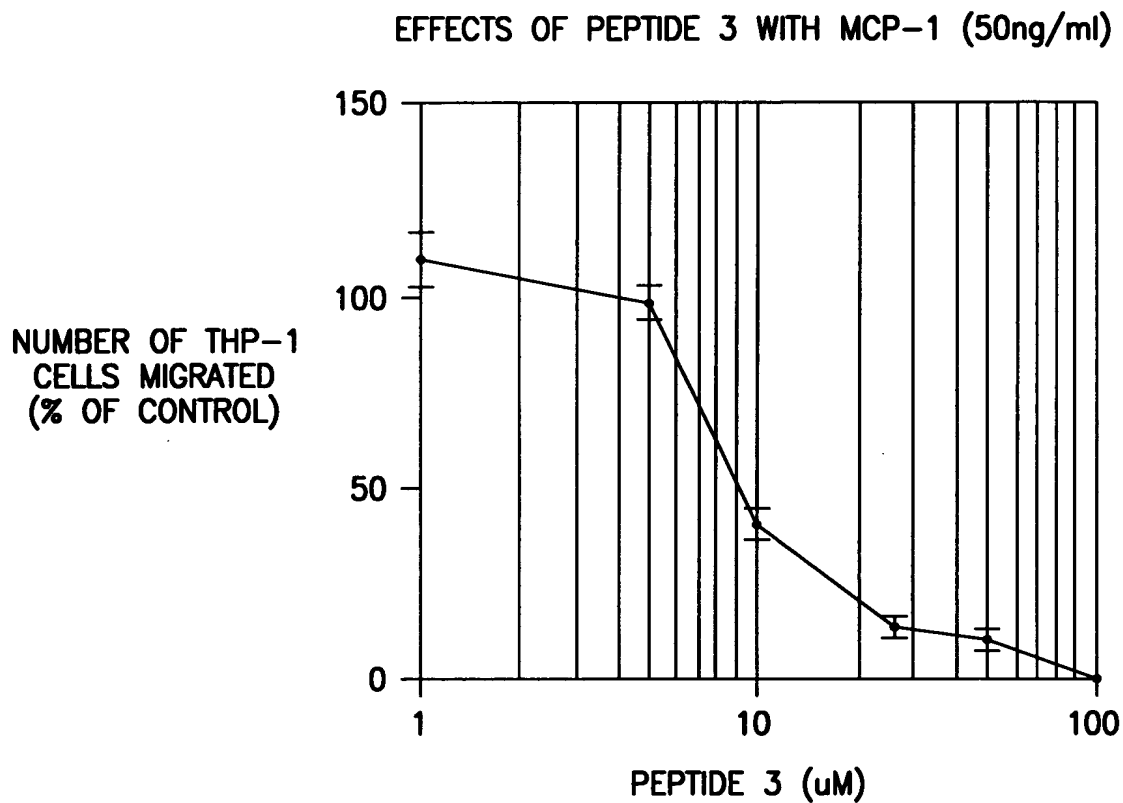


FIG. 2

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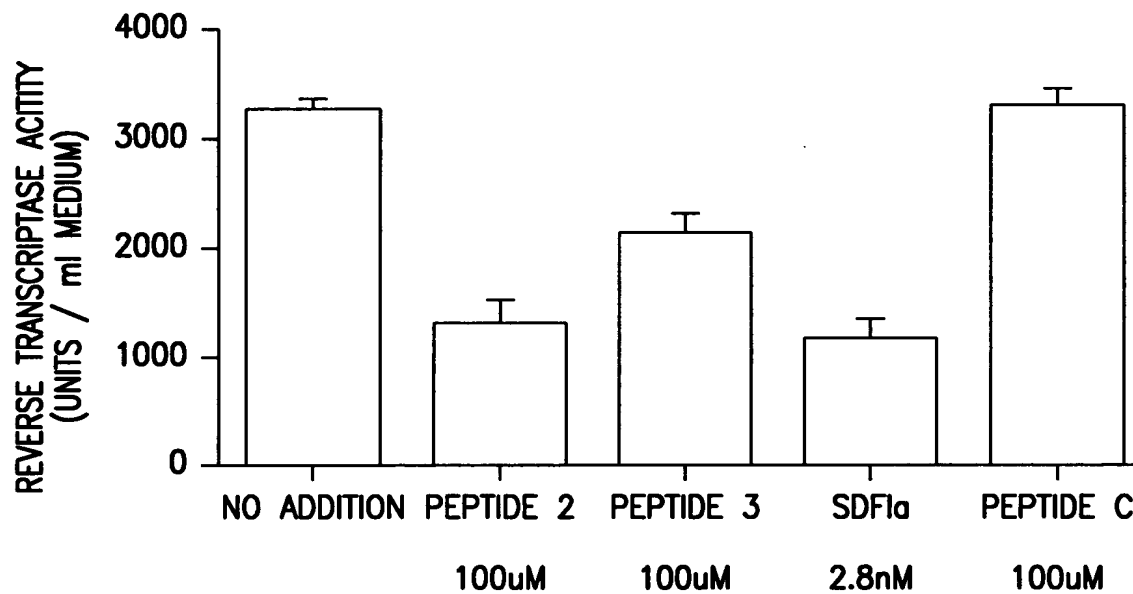


FIG. 3

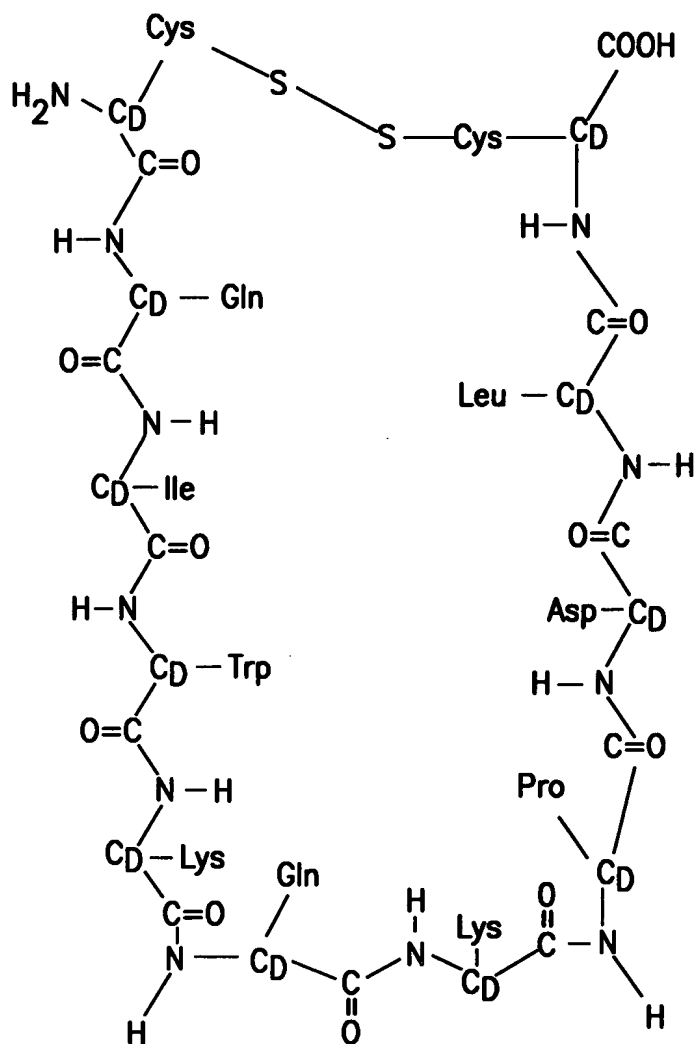


FIG. 4

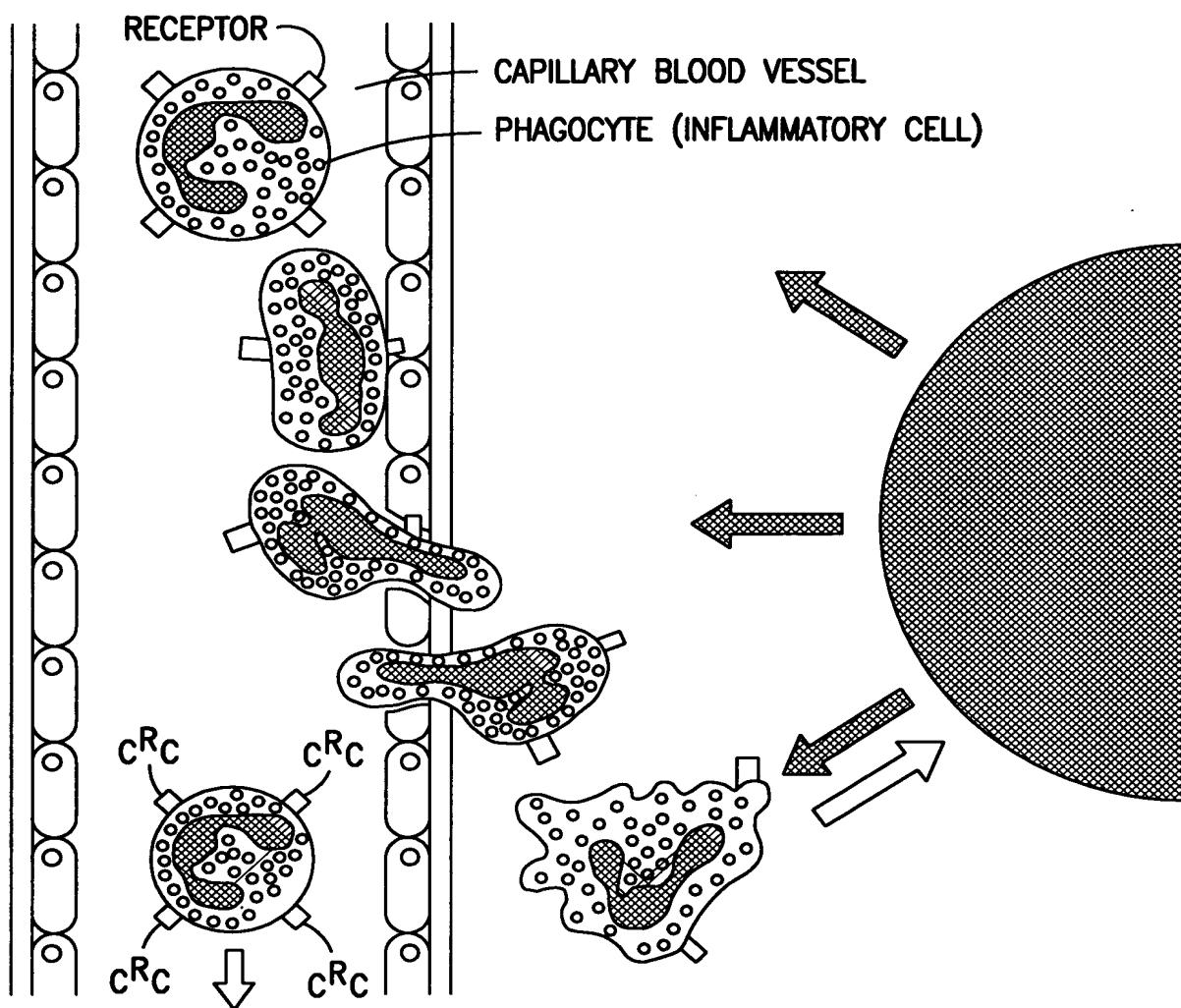


FIG. 5

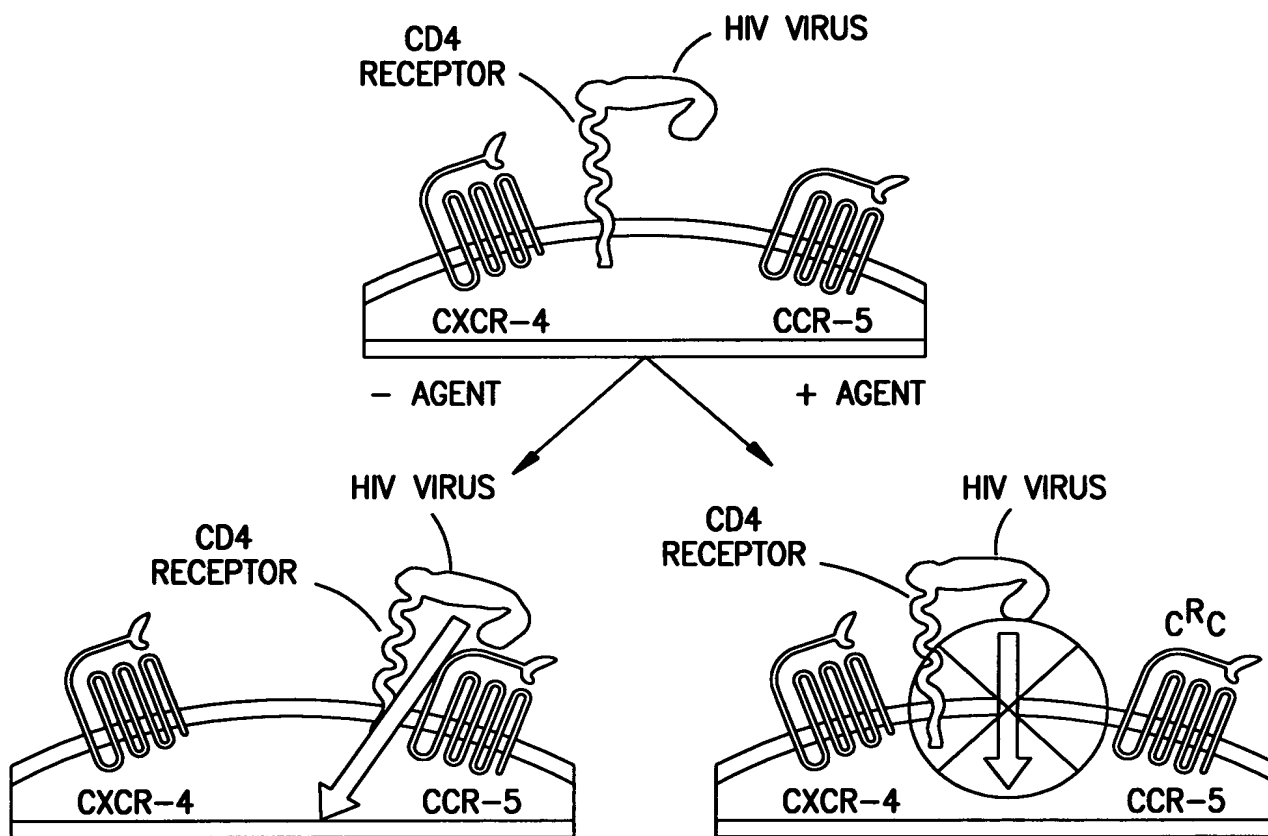
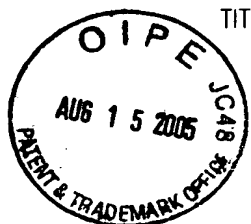


FIG. 6



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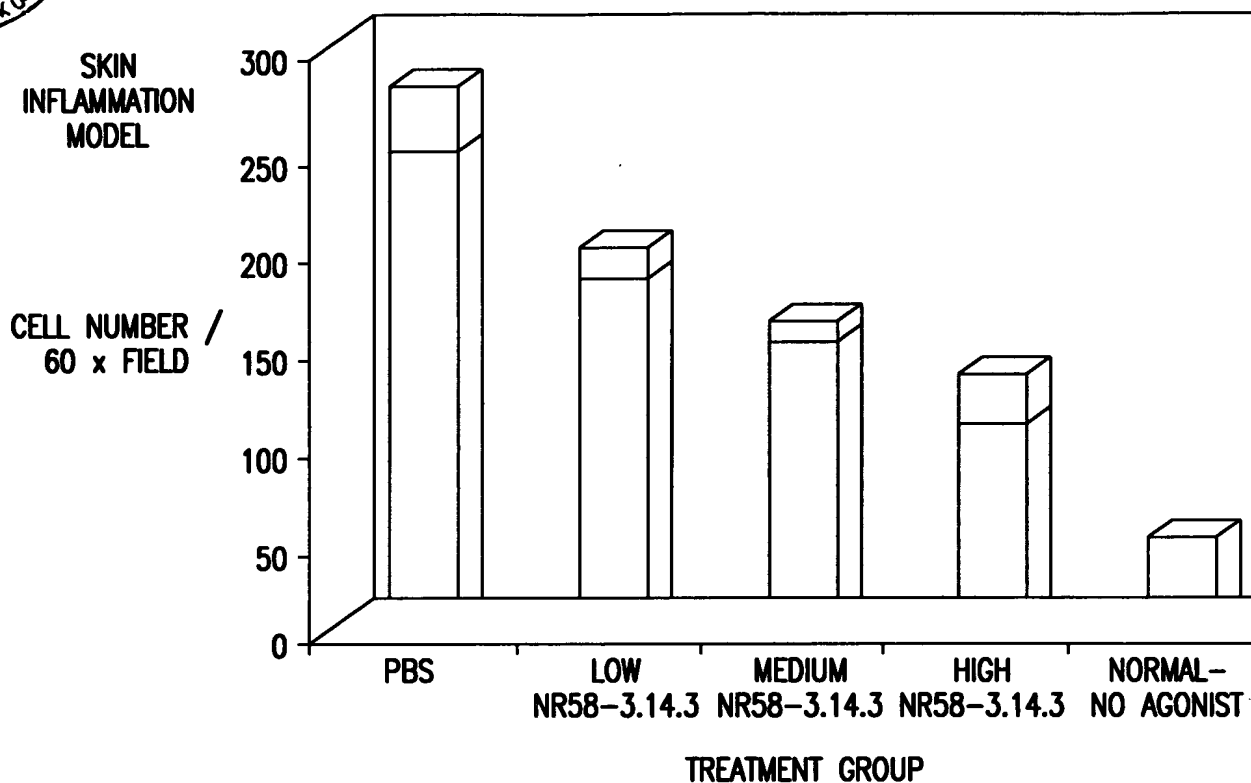


FIG. 7A

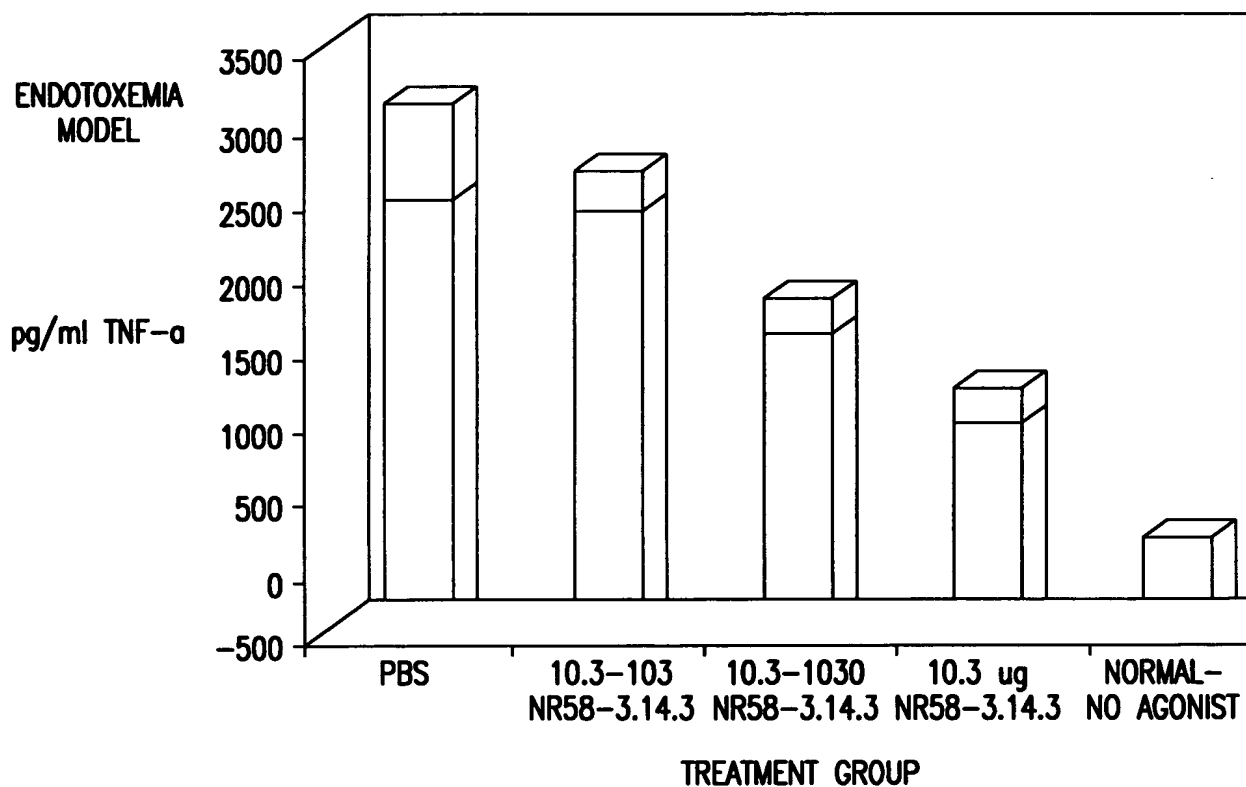


FIG. 7B

TITLE: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

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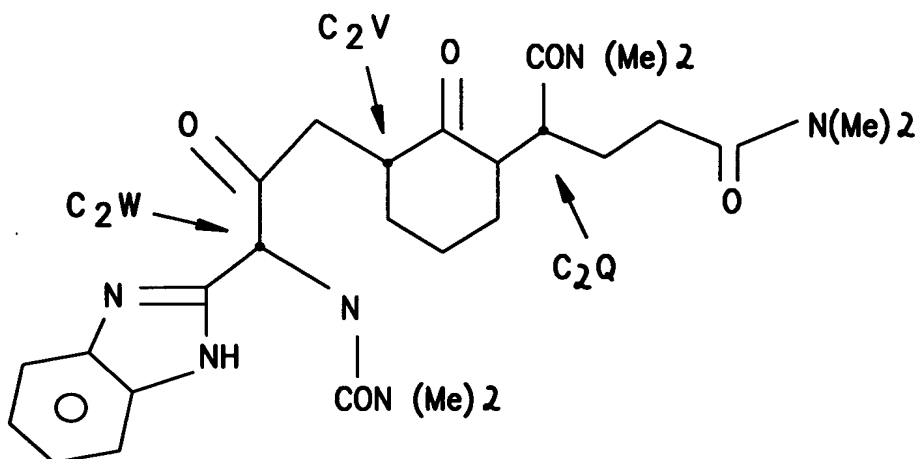


FIG. 8

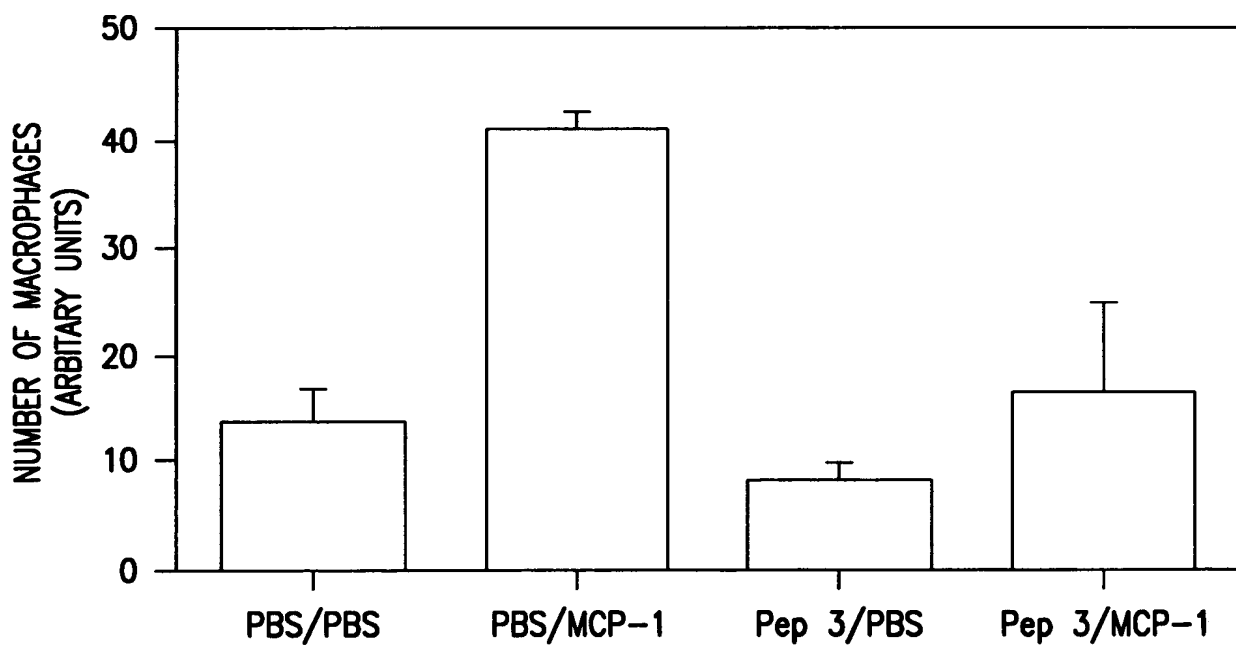


FIG. 9



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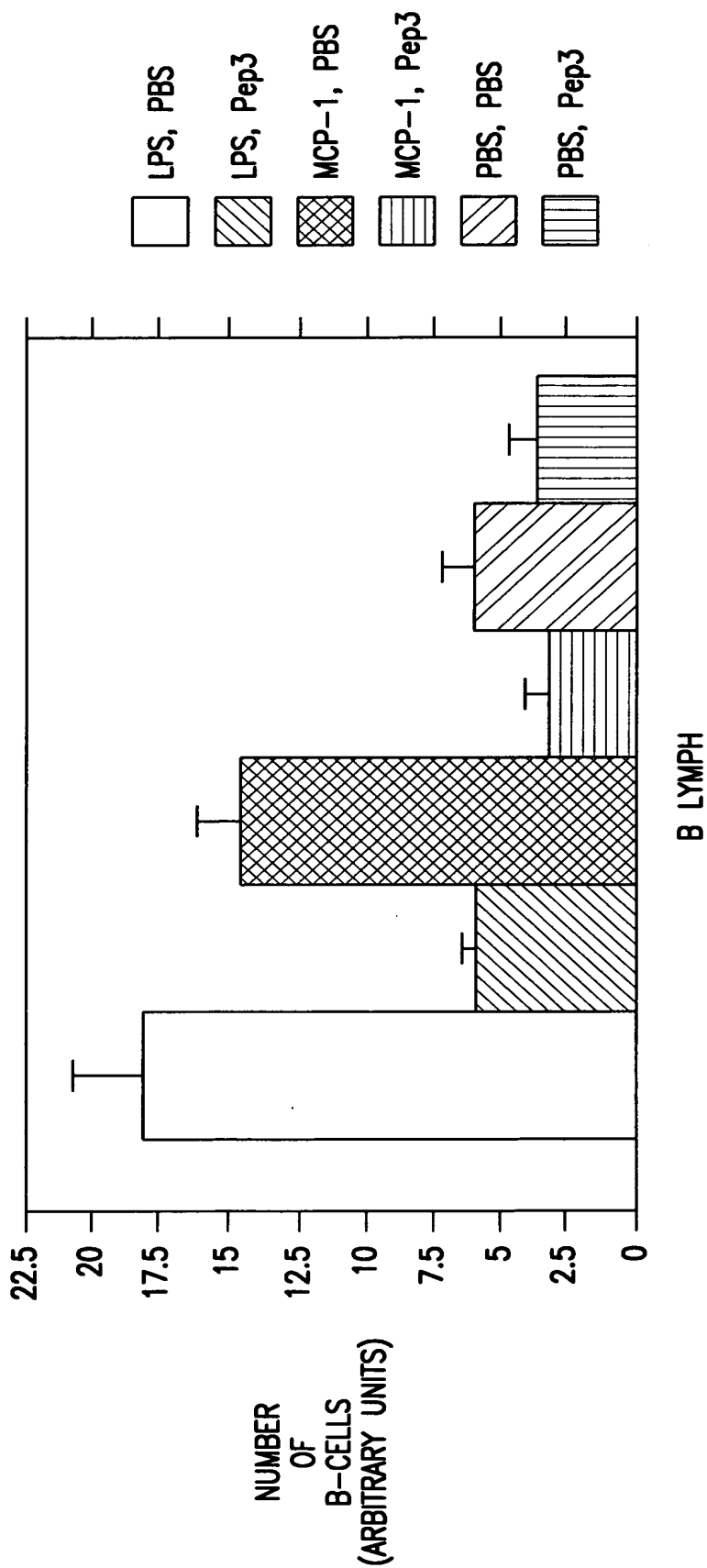


FIG. 10



TITLE: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

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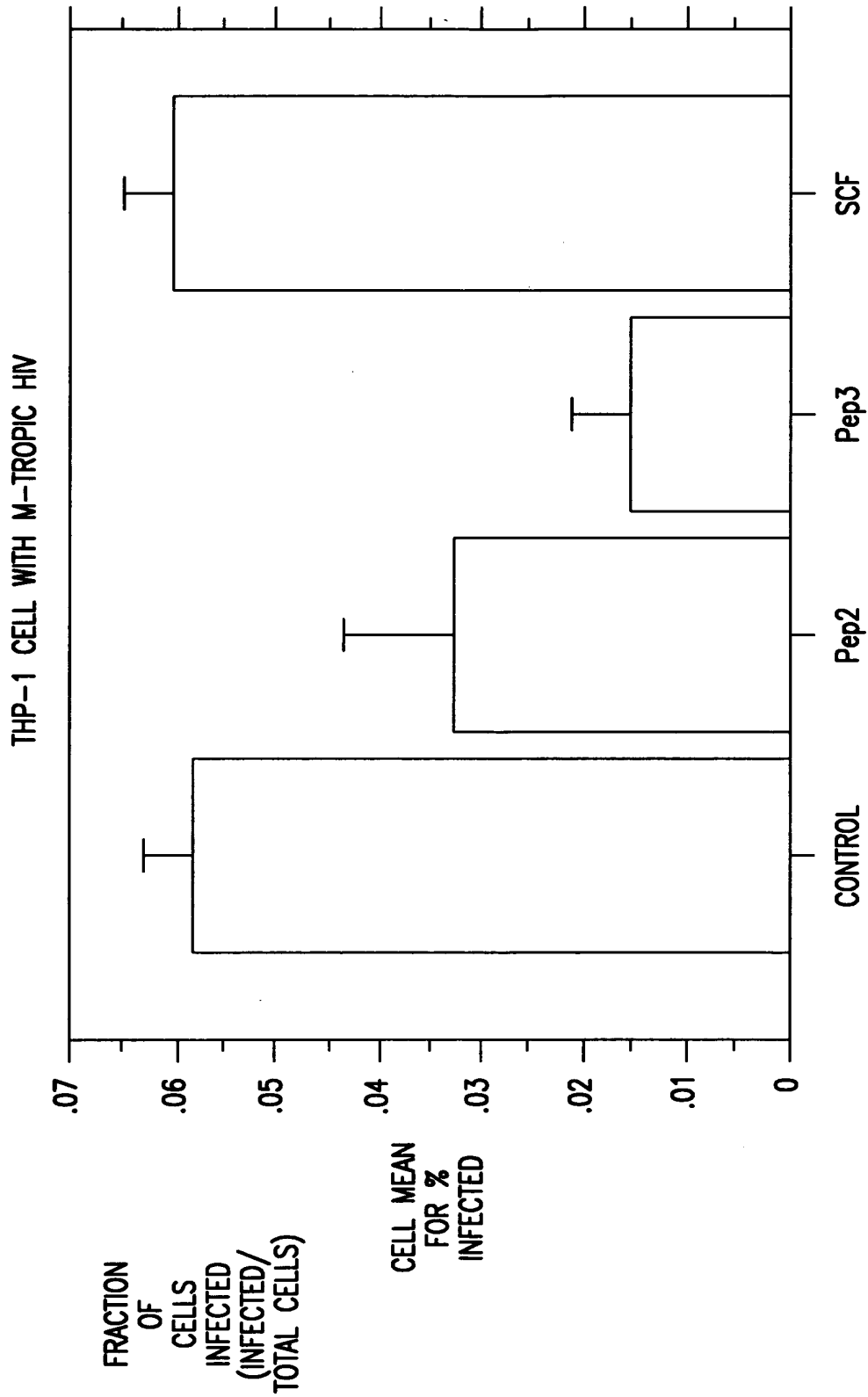


FIG. 11



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<u>Amino Acid</u>	<u>Codon</u>
Phe	UUU, UUC
Ser	UCU, UCC, UCA, UCG, AGU, AGC
Tyr	UAU, UAC
Cys	UGU, UGC
Leu	UUA, UUG, CUU, CUC, CUA, CUG
Trp	UGG
Pro	CCU, CCC, CCA, CCG
His	CAU, CAC
Arg	CGU, CGC, CGA, CGG, AGA, AGG
Gln	CAA, CAG
Ile	AUU, AUC, AUA
Thr	ACU, ACC, ACA, ACG
Asn	AAU, AAC
Lys	AAA, AAG
Met	AUG
Val	GUU, GUC, GUA, GUG
Ala	GCU, GCC, GCA, GCG
Asp	GAU, GAC
Gly	GGU, GGC, GGA, GGG
Glu	GAA, GAG

FIG. 12



TITLE: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

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<b>Original Residue</b>	<b>Exemplary Substitutions</b>	<b>Preferred Substitutions</b>
<b>Ala (A)</b>	<b>val; leu; ile</b>	<b>val</b>
<b>Arg (R)</b>	<b>lys; gln; asn</b>	<b>lys</b>
<b>Asn (N)</b>	<b>gln; his; lys; arg</b>	<b>gln</b>
<b>Asp (D)</b>	<b>glu</b>	<b>glu</b>
<b>Cys (C)</b>	<b>ser</b>	<b>ser</b>
<b>Gln (Q)</b>	<b>asn</b>	<b>asn</b>
<b>Glu (E)</b>	<b>asp</b>	<b>asp</b>
<b>Gly (G)</b>	<b>pro</b>	<b>pro</b>
<b>His (H)</b>	<b>asn; gln; lys; arg</b>	<b>arg</b>
<b>Ile (I)</b>	<b>leu; val; met; ala; phe norleucine</b>	<b>leu</b>
<b>Leu (L)</b>	<b>norleucine; ile; val; met; ala; phe</b>	<b>ile</b>
<b>Lys (K)</b>	<b>arg; gln; asn</b>	<b>arg</b>
<b>Met (M)</b>	<b>leu; phe; ile</b>	<b>leu</b>
<b>Phe (F)</b>	<b>leu; val; ile; ala</b>	<b>leu</b>
<b>Pro (P)</b>	<b>gly</b>	<b>gly</b>
<b>Ser (S)</b>	<b>thr</b>	<b>thr</b>
<b>Thr (T)</b>	<b>ser</b>	<b>ser</b>
<b>Trp (W)</b>	<b>tyr</b>	<b>tyr</b>
<b>Tyr (Y)</b>	<b>trp; phe; thr; ser</b>	<b>phe</b>
<b>Val (V)</b>	<b>ile; leu; met; phe; ala; norleucine</b>	<b>leu</b>

FIG. 13



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REPLACEMENT SHEET

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PEPTIDE-3

LFL peptide 3(1-12)[MCP-1]: Residues 50-61 of mature hMCP-1  
E-I-C-A-D-P-K-Q-K-W-V-Q (SEQ. ID. NO.: 1)  
L amino acids

LFL peptide 3(3-12)[MCPI] Residues 52-61 of mature hMCP-1  
C-A-D-P-K-Q-K-W-V-Q (SEQ. ID. NO.: 7)  
L amino acids

LFL peptide 3(1-6)[MCP1]: Residues 50-55 of mature hMCP-1  
E-I-C-A-D-P (SEQ. ID. NO.: 8)  
L amino acids

LFL peptide 3(7-12)[MCP1]: Residues 56-61 of mature hMCP-1  
K-Q-K-W-V-Q (SEQ. ID. NO.: 9)  
L amino acids

LFL Leu<sub>4</sub>peptide3(1-12)[MCP-1]  
E-I-C-L-D-P-K-Q-K-W-V-Q (SEQ. ID. NO.: 10)  
L amino acids

LFL Ser<sub>7</sub>peptide3(1-12)[MCP-1]  
E-I-C-A-D-P-S-Q-K-W-V-Q (SEQ. ID. NO.: 11)  
L amino acids

LFL Ile<sub>11</sub>peptide3(1-12)[MCP-1]  
E-I-C-A-D-P-K-Q-K-W-I-Q (SEQ. ID. NO.: 13)  
L amino acids

LFL Leu<sub>4</sub>Ile<sub>11</sub>peptide3(1-12)[MCP-1]  
E-I-C-L-D-P-K-Q-K-W-I-Q (SEQ. ID. NO.: 14)  
L amino acids

CFL Cys<sub>6</sub>Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub>peptide3(1-12)[MCP-1]  
C-E-I-C-L-D-P-K-Q-K-W-I-Q-C (SEQ. ID. NO.: 106)  
L amino acids

LRD Leu<sub>4</sub>Ile<sub>11</sub> peptide 3(1-12)[MCP-1]  
q-i-w-k-q-k-p-d-l-c-i-e  
D amino acids

FIG. 14A



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**CRD Cys<sub>6</sub>Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub>peptide 3(1-12)[MCP-1]**

**c-q-i-w-k-q-k-p-d-l-c-i-e-c**

**D amino acids**

**LFL Ser<sub>7</sub>Glu<sub>8</sub>Glu<sub>9</sub>peptide3(1-12)[MCP1]:Residues 50-61 of mature hMIP1 $\alpha$**

**E-I-C-A-D-P-S-E-E-W-V-Q (SEQ. ID. NO.: 12)**

**L amino acids**

**LFL peptide3(10-12)[MCP-1]**

**W-V-Q**

**L amino acids**

**CFL Cys<sub>6</sub>Cys<sub>4</sub> peptide3(10-12)[MCP-1]**

**C-W-V-Q-C (SEQ. ID. NO.: 107)**

**L amino acids**

**LRD peptide3(10-12)[MCP-1]**

**q-v-w**

**D amino acids**

**LFL peptide3(7-9)[MCP-1]**

**K-Q-K**

**L amino acids**

**LRD peptide3(7-9)[MCP-1]**

**k-q-k**

**D amino acids**

**LFL peptide 3(7-9)[MIP1 $\alpha$ ](MIP1 $\alpha$  specific inhibitor)**

**S-E-E**

**L amino acids**

**LRD peptide3(7-9)[MIP1 $\alpha$ ] (MIP1 $\alpha$  specific inhibitor)**

**e-e-s**

**D amino acids**

**LFL peptide3(7-9)[IL-8](IL-8 specific inhibitor)**

**K-E-N**

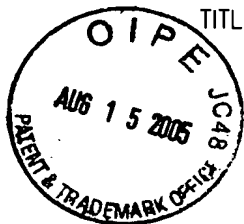
**L amino acids**

**LRD peptide3(7-9)[IL-8](IL-8 specific inhibitor)**

**n-e-k**

**D amino acids**

**FIG. 14B**



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REPLACEMENT SHEET

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**LFL peptide<sub>3</sub>(7-9)[SDF-1 $\alpha$ ](SDF-1 $\alpha$  specific inhibitor)**

**K-L-K**

**L amino acids**

**LRD peptide<sub>3</sub>(7-9)[SDF1 $\alpha$ ] (SDF-1 $\alpha$  specific inhibitor)**

**k-l-k**

**D amino acids**

**LFL Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub> peptide<sub>3</sub>(3-12)[MCP-1]**

**L-D-P-K-Q-K-W-I-Q-C (SEQ. ID. NO.: 84)**

**L amino acids**

**CRD Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub> peptide<sub>3</sub>(3-12)[MCP-1]**

**c-q-i-w-k-q-k-p-d-l-c**

**D amino acids**

**<sup>3</sup>H-Ala CRD-Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub> peptide<sub>3</sub>(3-12)[MCP-1](D-Ala attached to Asp residue of CRD-Leu<sub>4</sub>Ile<sub>11</sub>Cys<sub>13</sub> peptide<sub>3</sub>(3-12)[MCP-1])**

**<sup>3</sup>H-L-Leu LRD Cys<sub>13</sub> peptide<sub>3</sub>(3-12)[MCP-1]**

**c-q-i-w-k-q-k-p-d-L-c**

**D and L amino acids**

**LFL SES**

**S-E-S**

**L amino acids**

**LFL KKK**

**K-K-K**

**L amino acids**

**LFL Cys<sub>4</sub> peptide<sub>3</sub>(10-12)[MCP-1]**

**W-V-Q-C (SEQ. ID. NO.: 85)**

**L amino acids**

**LRD Cys<sub>4</sub> peptide<sub>3</sub>(10-12)[MCP-1]**

**c-q-v-w**

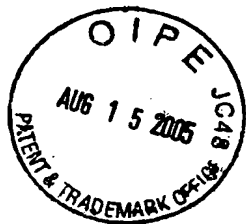
**D amino acids**

**LFL Ile<sub>11</sub>Cys<sub>13</sub> peptide<sub>3</sub>(10-12)[MCP-1]**

**W-I-Q-C (SEQ. ID. NO.: 86)**

**L amino acids**

**FIG. 14C**



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REPLACEMENT SHEET

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**LRD Cys<sub>13</sub>Ile<sub>11</sub>peptide3(10-12)[MCP-1]**

**cqiw**

**D amino acids**

**LRD peptide3(7-12)[MCP-1]**

**q-v-w-k-q-k**

**D amino acids**

**CFL Cys<sub>0</sub>Cys<sub>13</sub>peptide3(7-12)[MCP-1]**

**C-K-Q-K-W-V-Q-C (SEQ. ID. NO.: 108)**

**L amino acids**

**CRD Cys<sub>0</sub>Cys<sub>13</sub>peptide3(7-12)[MCP-1]**

**c-q-v-w-k-q-k-c**

**D amino acids**

**LFL peptide3(10-12)[RANTES]**

**WVR**

**L amino acids**

**LRD peptide3(10-12)[RANTES]**

**rvw**

**D amino acids**

**LFL peptide3(10-12)[SDF-1]**

**W-I-Q**

**L amino acids**

## **Peptide 2**

**LFL peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**

**S-Y-R-R-I-T-S-S-K-C-P-K-E-A-V (SEQ. ID. NO.: 105)**

**L amino acids**

**CFL Cys<sub>0</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**

**C-S-Y-R-R-I-T-S-S-K-C-P-K-E-A-V-C (SEQ. ID. NO.: 109)**

**L amino acids**

**LRD peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**

**v-a-e-k-p-c-k-s-s-t-i-r-r-y-s**

**D amino acids**

**FIG. 14D**



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**CRD Cys<sub>0</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**

**c-v-a-e-k-p-c-k-s-s-t-i-r-r-y-s-c**

**D amino acids**

**LFL peptide 2(1-15)[SDF1]: Residues 26-40 of mature hSDF-1 $\beta$**

**H-L-K-I-L-N-T-P-N-C-A-L-Q-I-V (SEQ. ID. NO.: 103)**

**L amino acids**

**CFL Cys<sub>0</sub>Cys<sub>16</sub>peptide 2(1-15)[SDF1]: Residues 26-40 of mature hSDF-1 $\beta$**

**C-H-L-K-I-L-N-T-P-N-C-A-L-Q-I-V-C (SEQ. ID. NO.: 110)**

**L amino acids**

**LRD peptide 2(1-15)[SDF1]: Residues 26-40 of mature hSDF-1 $\beta$**

**v-i-q-l-a-c-n-p-t-n-l-i-k-l-h**

**D amino acids**

**CRD Cys<sub>0</sub>Cys<sub>16</sub>peptide 2(1-15)[SDF1]: Residues 26-40 of mature hSDF-1 $\beta$**

**c-v-i-q-l-a-c-n-p-t-n-l-i-k-l-h-c**

**D amino acids**

**LFL peptide 2(1-14)[MIP-1 $\alpha$ ]: Residues 28-41 of hMIP-1 $\alpha$**

**D-Y-F-E-T-S-S-Q-C-S-K-P-G-V (SEQ. ID. NO.: 5)**

**L amino acids**

**LRD peptide 2(1-14)[MIP1 $\alpha$ ]: Residues 28-41 of mature hMIP1 $\alpha$**

**v-g-p-k-s-c-q-s-s-t-e-f-y-d**

**D amino acids**

**LFL peptide 2(1-16)[IL8]: Residues 27-42 of mature hIL8**

**E-L-R-V-I-E-S-G-P-H-C-A-N-T-E-I (SEQ. ID. NO.: 6)**

**L amino acids**

**LFL Peptide 2(1-10)[MCP-1]: Residues 28-37 of hMCP-1**

**S-Y-R-R-I-T-S-S-K-C (SEQ. ID. NO.: 87)**

**L amino acids**

**LFL peptide 2(10-15)[MCP-1]: Residues 37-42 of hMCP-1**

**C-P-K-E-A-V (SEQ. ID. NO.: 88)**

**L amino acids**

**LFL peptide 2(1-5)[MCP-1]: Residues 28-32 of hMCP-1**

**S-Y-R-R-I (SEQ. ID. NO.: 89)**

**L amino acids**

**FIG. 14E**

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**LFL peptide 2(6-10)[MCP-1]: Residues 33-37 of hMCP-1**  
**T-S-S-K-C (SEQ. ID. NO.: 90)**  
**L amino acids**

**LFL peptide 2(1-9)[MIP-1 $\alpha$ ]: Residues 28-36 of hMIP-1 $\alpha$**   
**D-Y-F-E-T-S-S-Q-C (SEQ. ID. NO.: 91)**  
**L amino acids**

**LFL peptide 2(9-14)[MIP-1 $\alpha$ ]: Residues 36-41 of hMIP-1 $\alpha$**   
**C-S-K-P-G-V (SEQ. ID. NO.: 92)**  
**L amino acid**

**LFL Cys<sub>0</sub>Ser<sub>10</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**  
**C-S-Y-R-R-I-T-S-S-K-S-P-K-E-A-V-C (SEQ. ID. NO.: 93)**  
**L amino acids**

**CFL Cys<sub>0</sub>Ser<sub>10</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**  
**C-S-Y-R-R-I-T-S-S-K-S-P-K-E-A-V-C (SEQ. ID. NO.: 111)**  
**L amino acids**

**LRD Cys<sub>0</sub>Ser<sub>10</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**  
**c-v-a-e-k-p-s-k-s-s-t-i-r-r-y-s-c**  
**D amino acids**

**CRD Cys<sub>0</sub>Ser<sub>10</sub>Cys<sub>16</sub>peptide 2(1-15)[MCP-1]: Residues 28-42 of hMCP-1**  
**c-v-a-e-k-p-s-k-s-s-t-i-r-r-y-s-c**  
**D amino acids**

**FIG. 14F**

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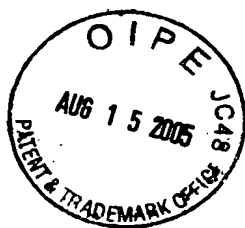
SEQUENCE	DARC BINDING	THP-1 MIGRATION		
		MCP-1	MIP-1 $\alpha$	SDF-1 $\alpha$
SYRRITSSKCPKEAV	350nM	ns	ns	ns
VAEKPCSSTIRRYIS	18 $\mu$ M	ns	ns	ns
SYRRITSK	22 $\mu$ M	ns	ns	ns
SYRRI	>100 $\mu$ M	ns	ns	ns
TSSKC	>100 $\mu$ M	ns	ns	ns
CPKEAV	>100 $\mu$ M	ns	ns	ns
HLKILNTPNCALQIV	19 $\mu$ M	10 $\mu$ M	40 $\mu$ M	7 $\mu$ M
DYFETSSQCSKPGV	>100 $\mu$ M	ns	ns	ns
VGPKSCQSSTEFYD	>100 $\mu$ M	ns	ns	ns
DYFETSSQC	>100 $\mu$ M	ns	ns	ns
CSKPGV	>100 $\mu$ M	ns	ns	ns

FIG 15



SEQUENCE	MOL WT.	DUFFY BINDING BD-50	MCP-1 ED-50	MIP-1 $\alpha$ ED-50	RANTES ED-50	SDF-1 $\alpha$ ED-50	IL-8 ED-50	OTHER DATA
AQPDAINAPVTCC	1302	90 $\mu$ M	ns	ns	-	ns	ns	
SYRRITSSKCPKEAV	1725	100 $\mu$ M	ns	ns	-	ns	-	
VAEKPCCKSSTIRRY	1725	18 $\mu$ M	ns	ns	-	ns	-	
HLKILNTPNCALQIV	1677.3	19 $\mu$ M	10 $\mu$ M	40 $\mu$ M	-	7 $\mu$ M	-	
DYFETSSQCSKPGV	1549	>100 $\mu$ M	ns	ns	-	ns	-	
VQPKSCQSSTEFYD	1549	>100 $\mu$ M	ns	ns	-	ns	-	
SYRRITSSKC	1097.4	22 $\mu$ M	ns	ns	-	ns	-	
CPKEAV	645.8	>100 $\mu$ M	ns	ns	-	ns	-	
SYRRI	693.9	>100 $\mu$ M	ns	ns	-	ns	-	
TSSKC	525.7	>100 $\mu$ M	ns	ns	-	ns	-	
DYFETSSQC	1079.2	>100 $\mu$ M	ns	ns	-	ns	-	
CSKPGV	589.8	>100 $\mu$ M	ns	ns	-	ns	-	

FIG. 16A



SICADPKQKNVQ	1445	6 $\mu$ M	8 $\mu$ M	7.5 $\mu$ M	-	13.5 $\mu$ M	10 $\mu$ M	
CADPKQKNVQ	1202	-	8 $\mu$ M	6.5 $\mu$ M	-	9 $\mu$ M	8.5 $\mu$ M	
CQVWKQKPDAC	1305	3 $\mu$ M	100nM	-	-	-	-	
CQVWKQKPDAC	1305	40 $\mu$ M	30nM	-	-	-	-	
BICADP	647	-	25 $\mu$ M	20 $\mu$ M	-	18.5 $\mu$ M	16 $\mu$ M	
KQKVVQ	816	15 $\mu$ M	7 $\mu$ M	5 $\mu$ M	-	5.5 $\mu$ M	5 $\mu$ M	
BICLDPKQKVVQ	1487	-	8 $\mu$ M	7 $\mu$ M	-	2.5 $\mu$ M	3 $\mu$ M	
EICADPSQKVVQ	1404	25 $\mu$ M	7 $\mu$ M	5.5 $\mu$ M	-	4 $\mu$ M	3 $\mu$ M	
EICADPKQKWIQ	1459	-	5.5 $\mu$ M	3.5 $\mu$ M	-	7 $\mu$ M	2 $\mu$ M	
EICLDPKQKWIQ	1501	90 $\mu$ M	2 $\mu$ M	2 $\mu$ M	-	4 $\mu$ M	3.5 $\mu$ M	
WVQ	431.5	1 $\mu$ M	8 $\mu$ M	7.5 $\mu$ M	1.5 $\mu$ M	2.25 $\mu$ M	1 $\mu$ M	
KQK	464.5	50 $\mu$ M	7 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	
SEE	399.4	>100 $\mu$ M	>100 $\mu$ M	-	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	
KEN	425.4	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	>100 $\mu$ M	-	

FIG.16B

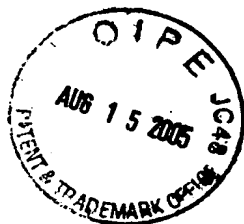


KLK	516.6	>100μM	>100μM	>100μM	>100μM	—	>100μM	
CQIWKQKPDLC	1359	>100μM	—	—	—	350nM	10nM	NOTE 1
CQIWKQKPDLC	1448	—	—	—	—	—	—	NOTE 2
CQIWKQKPDLC	1472.2	—	—	—	—	—	—	
SES	357.3	>100μM	—	—	—	—	—	
KKK	609.8	>100μM	—	—	—	—	—	

NOTE 1: IN VIVO EFFECT ABOLISHES MACROPHAGES IN AN IN VIVO RATE INTRADEMAL STUDY INDUCED BY 500 ng MCP-1, 300 g IV, AND 10mg SQ 30 MINUTES PRIOR TO MCP-1, D-ALA ("a") IS ATTACHED TO D-ASP ("d").

NORE 2: IN SAME STUDY AS NOTE 1 ABOVE, NO EFFECT ON MACROPHAGES SEEN

**FIG. 16C**



TITLE: COMPOUNDS AND METHODS TO INHIBIT OR AUGMENT AN INFLAMMATORY RESPONSE

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SERIAL NO.: 09/150,813 DOCKET NO.: 1543.002US1

23/23

STUDY DESIGN TABLE

GROUP	ANIMAL#	N	RX	RX DOSE/ROUTE T=30 MIN	DERMAL AGONIST	DERMAL AGONIST DOSE (ng IN 50 ul) T=0	HOUR OF SACRIFICE
1	1,2,3	3	PBS	200 ul:LV 200 ul:SQ BACK	PBS LPS MCP-1 MCP-1	0 50 100 500	20-24
2	4,5,6	3	NR58-3.14.3	3 ug:LV 100 ug:SQ BACK	PBS LPS MCP-1 MCP-1	0 50 100 500	20-24
3	7,8,9	3	NR58-3.14.3	30 ug:LV 1 mg:SQ BACK	PBS LPS MCP-1 MCP-1	0 50 100 500	20-24
4	10,11,12	3	NR58-3.14.3	300 ug:LV 10 mg:SQ BACK	PBS LPS MCP-1 MCP-1	0 50 100 500	20-24

FIG. 17